Bensimon et al. (U.S. Patent No. 5,866,328). Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden by showing, first, that the cited prior art coupled with the general knowledge at the time of the invention must contain some suggestion or incentive to motivate a skilled artisan to modify or combine references. *See In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the Examiner must show that the modification or combination of prior art references must have a reasonable expectation of success (at the time of the invention). *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the Examiner must show that the cited or combined references teach each and every limitation of the claims. *See In re Zurko,* 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

The Examiner has asserted that Southern et al. teaches a method for sequencing DNA comprising all of the features of claim 21. The Examiner has acknowledged that Southern et al., however, does not teach the feature of the present invention where a

heterogeneous population of single-stranded DNA is immobilized in a unique amount in the same reaction zone. The Examiner has asserted that Bensimon et al. discloses this feature.

The key difference between the present invention and the disclosure of Southern et al. is that the present method of sequencing DNA allows a heterogeneous population of **single stranded** DNAs to be sequenced when they are immobilized in a unique amount in the same reaction zone.

Contrary to the Examiner's assertion, Bensimon et al. does not teach a method wherein a heterogeneous population of a **single stranded** DNA is immobilized in a unique amount in the same reaction zone. In fact, Bensimon et al. describes the use of atomic force (AFM) microscopy for sequencing **double stranded** DNA. This method requires that an individual double stranded nucleic acid is attached to the AFM device, which comprises a movable lever close to the sample surface. One strand of the double stranded DNA molecule is attached to the sample surface and the other strand of the double stranded DNA is attached to the movable lever. The energy required to move the lever, and thereby separate the strands, can be used to determine the sequence of the nucleic acid molecule.

The nucleic acid molecules of Bensimon et al. are not immobilized in the same reaction zone. It is clear from Bensimon et al. that only one sequence at a time can be analyzed in the AFM device. Column 7, lines 27-30, of Bensimon et al. states that the heterogeneous population of DNA molecules are tested in series, by coupling them one

after another to the measuring surface. Therefore, the DNA molecules are coupled to the surface at separate locations, so that they can be individually sequenced in separate steps. In contrast, step (a) of claim 21 of the present invention requires that each of the single stranded DNAs is immobilized in the same reaction zone, such that the sequence of each of the single stranded DNAs in the population can be determined together in the same reaction steps (b) to (g). Thus, in certain embodiments of the present invention, the sequence of each of the DNA may be determined simultaneously. The DNA molecules of Bensimon et al. are not immobilized in the same reaction zone according to claim 21 of the present invention because the sequence of the DNAs is not determined together in the same reaction step or series of steps.

In the Advisory Action dated August 1, 2001, the Examiner stated that "Applicants argues that because Bensimon has a preferred embodiment of sequencing DNA in series by coupling them one after another, Bensimon is limited to the preferred embodiment." Further, the Examiner quotes two passages from section 2123 of the M.P.E.P.: "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 169 USPQ 423 (CCPA 1971)" and "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including nonpreferred embodiments. Merk & Co. v. Biocraft Laboratories, 10 USPQ2d 1843 (Fed. Cir. 1989)."

The court in *In re Susi* held that a disclosed embodiment that is identified in the specification as the "most preferred embodiment" does not teach away from other disclosed embodiments within the same application that are identified as "preferred" or "more preferred" or "less preferred." In footnote 3 of *In re Susi*, the court stated that:

> Appellant also argues that Knapp teaches away from his invention because, while the formula set forth in the discussion of Knapp . . . is referred to as a "particularly preferred embodiment," Knapp terms a particular subclass of the compounds represented by the formula, which subclass is not as close structurally to appellant's additives as are other species within the "particulary preferred" class, [as] his "most particulary preferred embodiment[s]." We cannot accept the suggestion that one is significantly "taught away" from a "particularly preferred embodiment" by the suggestion . . . that something else may be even better.

In other words, the court has stated that disclosed "preferred" embodiments do not teach away from other disclosed less preferred embodiments (both embodiments must be disclosed).

The Examiner has stated that "it is clear that simply because Bensimon has a preferred embodiment of sequencing DNA in series by coupling them one after another, this embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and that this does not constitute a teaching away." Applicants respectfully disagree. Bensimon does not disclose these broader embodiments.

The Examiner appears to be suggesting that there are other embodiments disclosed in Bensimon which do relate to immobilizing a heterogeneous population of single stranded

DNAs in a unique amount in the same reaction zone. As an example of a broader embodiment taught by Bensimon, the Examiner refers to Figure 1 and column 7, line 62 to column 8, line 17 which purportedly show at least two strands of single stranded DNA immobilized in the same reaction zone. Applicants respectfully disagree.

Figure 1 of Bensimon does not depict at least two strands of single stranded DNA. Column 10, lines 10-18, of Bensimon state that:

> In order to pull a single strand of a DNA dimer (aa'), as shown diagrammatically in FIG. 1, one of it ends is anchored to a pretreated flat surface α via a link by means of functionalization with an amine group A, and the other end is anchored to a streptaviden-coated Dynal magnetic bead B. A small magnet stuck to the end of the lever of an AFM enables linkage between the lever and the Dynal bead to be maintained. Since the two strands a and a' are complementary, they are partially paired.

It is clear from this passage that Bensimon is sequencing double stranded DNA (i.e., DNA dimers (aa')). Figure 1 shows a partially paired DNA dimer with one strand of the dimer attached to one plate of the AFM device and the other strand attached to the other plate of the AFM device. The loop structure at the other end of the double stranded DNA molecule is necessary to "prevent the strands from dissociating at the end of the operation, so that [the operation] can be repeated if appropriate." See column 7, lines 32-38. Further, assuming, *arguendo*, that the DNA depicted in Figure 1 is single stranded DNA, it is one single stranded molecule not "at least two" as stated by the Examiner.

In addition, the Examiner refers to column 7, line 62 to column 8, line 17, of Bensimon. This passage also discusses double stranded DNA. In particular, column 7, lines 62-63, states that "[a] double stranded DNA is converted to a dimer aa'/a'a through the addition of complementary oligonucleotides . . . . " Further, column 8, lines 9-17, states that the two DNA strands are first dissociated and then, because the strands are complementary, the strands rejoin or pair spontaneously. This paired double stranded DNA is then sequenced by attaching the ends to separate plates of the AFM and "unwinding" or unpairing the strands to produce a measurable force. In order for unwinding to take place the strands must be paired (i.e., double stranded DNA).

Furthermore, Applicants submit that because the sequencing method of Bensimon relies on measuring the energy released of base pairs of DNA, only **double stranded** DNA can be used. Column 3, lines 8-12, of Bensimon states that:

"[t]he invention is based on the demonstration that it is possible to measure, quickly and reliably, the bonding force of each base pair of a double-stranded DNA or of a DNA/RNA hybrid and to assign a specific sequence to each of these values . . . ." (Emphasis added).

Further, column 4, lines 21-28, of Bensimon states that:

> the energy of unpairing between each base pair of the DNA or DNA/RNA hybrid is determined by attaching at least one base of each strand of the DNA or of the DNA/RNA hybrid to a support and moving away the supports so as to pull apart, one after another, each base pair while measuring at each unpairing the energy needed for unpairing and comparing it with predetermined values.

Thus, Bensimon, like Southern, does not teach each and every element of the claimed invention. In particular, Bensimon does not teach a method wherein a heterogeneous population of single stranded DNA is immobilized in a unique amount in the same reaction zone.

Applicants submit that there is no suggestion or incentive to motivate the skilled artisan to combine the teaching of Bensimon et al. with Southern et al. as the techniques involved in the references are wholly unrelated to each other. The methods of Southern et al. are dependent on a series of chemical and enzymatic steps. In contrast, the method of Bensimon et al. utilizes a physical method of measuring the base pairing energy. Further, the method of Bensimon et al., which involves the immobilization of a number of DNA molecules on a solid support, is particularly adapted to the use of this physical method. The DNA molecules are only immobilized on the solid surface in Bensimon et al. in order to allow them to be attached to the AFM device so that their strands are separated. There is no suggestion whatsoever in Bensimon et al. that there is any particular advantage associated with immobilizing a population of heterogeneous DNA molecules in any particular way which may be transferable to a chemical or enzymatic method of DNA sequencing. The "express advantages," which the Examiner suggests are noted by Bensimon et al. in relation to their method, do not result solely from an independent feature of immobilizing a heterogeneous population of DNAs on a solid support, but only from

doing so in the context of atomic force microscopy. Therefore, one of ordinary skill in the art would not be motivated to combine the teachings of Southern et al. with that of Bensimon et al.

Thus, when combining the cited references, the skilled artisan is left with two different methods to sequence DNA (one which is dependent on a series of chemical and enzymatic steps and the other which is dependent on pulling double stranded DNA apart with an atomic force microscope and measuring the energy). There is no way to combine the features of these two methods to arrive at the present invention. Further, there is no teaching in either reference to even suggest such a combination.

Therefore, because there is no suggestion or incentive to motivate a skilled artisan to modify or combine references and because the references, singly or in combination, fail to teach each and every limitation of the claims, Applicants respectfully request withdrawal of the rejection of claims 21-32 under 35 U.S.C. § 103(a).

Claims 21-25 and 27-32 have been rejected under 35 U.S.C. § 103(a) over Macevicz et al. (PCT Publication No. WO 96/33205) in view of Bensimon et al. Applicants respectfully traverse this rejection.

The Examiner has asserted that Macevicz et al. teaches a method for sequencing DNA comprising all of the features of claim 21. The Examiner has acknowledged that Macevicz et al. does not teach the feature where a heterogeneous population of single-

stranded DNA is immobilized in a unique amount in the same reaction zone. The Examiner has asserted that Bensimon et al. discloses this feature.

The key difference between the present invention and the disclosure of Macevicz et al. is that the present method of sequencing DNA allows a heterogeneous population of single stranded DNAs to be sequenced when they are immobilized in a unique amount in the same reaction zone.

As discussed above, Bensimon et al. does not teach a method wherein a heterogeneous population of a single stranded DNA is immobilized in a unique amount in the same reaction zone.

Moreover, there is no suggestion or incentive to motivate the skilled artisan to combine the teaching of Bensimon et al. with Macevicz et al. as the techniques involved in the references are wholly unrelated to each other. The methods of Macevicz et al. are dependent on a series of chemical and enzymatic steps. In contrast, the method of Bensimon et al. utilizes a physical method of measuring the base pairing energy. Further, the method of Bensimon et al., which involves the immobilization of a number of DNA molecules on a solid support, is particularly adapted to the use of this physical method. The DNA molecules are only immobilized on the solid surface in Bensimon et al. in order to allow them to be attached to the AFM device so that their strands are separated. As noted above, there is no suggestion whatsoever in Bensimon et al. that there is any

particular advantage associated with immobilizing a population of heterogeneous DNA molecules in any particular way which may be transferable to a chemical or enzymatic method of DNA sequencing. Again, the "express advantages," which the Examiner suggests are noted by Bensimon et al. in relation to their method, do not result solely from an independent feature of immobilizaing a heterogeneous population of DNAs on a solid support, but only from doing so in the context of atomic force microscopy. Therefore, one of ordinary skill in the art would not be motivated to combine the teachings of Macevicz et al. with that of Bensimon et al.

Thus, when combining the cited references, the skilled artisan is left with two different methods to sequence DNA (one which is dependent on a series of chemical and enzymatic steps and the other which is dependent on pulling double stranded DNA apart with an atomic force microscope and measuring the energy). There is no way to combine the features of these two methods to arrive at the present invention. Further, there is no teaching in either reference to even suggest such a combination.

Therefore, because there is no suggestion or incentive to motivate a skilled artisan to modify or combine references and because the references, singly or in combination, fail to teach each and every limitation of the claims, Applicants respectfully request withdrawal of the rejection of claims 21-25 and 27-32 under 35 U.S.C. § 103(a).

Claims 21-39 and 41-43 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Southern et al. in view of Bensimon et al. and further in view of Stratagene Catalog (1988, page 39). Applicants respectfully traverse this rejection.

The Examiner has stated that Southern et al. in view of Bensimon et al. teaches the method of claims 21-32. The Examiner acknowledges that Southern et al. and Bensimon et al. provide no motivation to combine all the reagents for identifying a base at a target position in a single-stranded sample DNA sequence in the form of a kit.

The reasons why the combination of Southern et al. and Bensimon et al. does not render the claimed invention obvious are discussed in detail above.

Briefly, the key difference between the present invention and the disclosure of Southern et al. is that Southern et al. does not teach a method of sequencing DNA where a heterogeneous population of single stranded DNAs to be sequenced are immobilized in a unique amount in the same reaction zone. This deficiency in Southern et al. cannot be remedied by the teachings of Bensimon et al. As mentioned above, Bensimon et al. does not teach a method wherein a heterogeneous population of a single stranded DNA is immobilized in a unique amount in the same reaction zone. In fact, Bensimon et al. describes the use of atomic force (AFM) microscopy for sequencing double stranded DNA.

The DNA molecules of Bensimon et al. are not immobilized in the same reaction zone according to claim 21 of the present invention because the sequence of the DNAs is

not determined together in the same reaction step or series of steps. It is clear from Bensimon et al. that only one sequence at a time can be analyzed in the AFM device. Therefore, the double stranded DNA molecules are coupled to the surface at separate locations, so that they can be individually sequenced in separate steps.

Moreover, there is no suggestion or incentive to motivate the skilled artisan to combine the teaching of Bensimon et al. with Southern et al. as the techniques involved in the references are wholly unrelated to each other. The methods of Southern et al. are dependent on a series of chemical and enzymatic steps. In contrast, the method of Bensimon et al. utilizes a physical method of measuring the base pairing energy. The DNA molecules are only immobilized on the solid surface in Bensimon et al. in order to allow them to be attached to the AFM device so that each strand of the double stranded DNA can be separated. Therefore, one of ordinary skill in the art would not be motivated to combine the teachings of Southern et al. with that of Bensimon et al.

Further, the combination of Southern et al. with Bensimon et al. and the Stratagene Catalog also fail to rendered claims 21-39 and 41-43 of the present invention obvious.

Therefore, because there is no suggestion or incentive to motivate a skilled artisan to modify or combine references and because the references, singly or in combination, fail to teach each and every limitation of the claims, Applicants respectfully request withdrawal of the rejection of claims 21-39 and 41-43 under 35 U.S.C. § 103(a).

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned agent concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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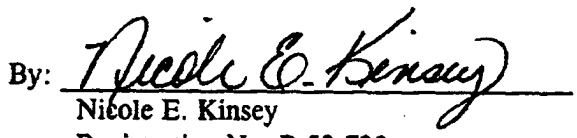
By: 
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